PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference C1-A0416Y1P	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2006/306800	International filing date *(day/month/year)* 31 March 2006 (31.03.2006)	Priority date *(day/month/year)* 31 March 2005 (31.03.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 03 October 2007 (03.10.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference C1-A0416Y1P	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2006/306800	31.03.2006	31.03.2005

International Patent Classification (IPC) or both national classification and IPC

Applicant
CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306800

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ the translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed

☐ filed together with the international application in electronic form

☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306800

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-44	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-44	NO
Industrial applicability (IA)	Claims	1-44	YES
	Claims		NO

2. Citations and explanations:

Document 1.
KIPRIYANOV SM. et al., Effect of domain order on the activity of bacterially produced bispecific single-chain Fv antibodies., J. Mol. Biol., 2003, Vol. 330, No. 1, pages 99-111
Document 2.
KRIANGKUM J. et al., Bispecific and bifunctional single chain recombinant antibodies., Biomol. Eng., 2001, Vol. 18, No. 2, pages 31-40
Document 3:
DE JONGE J. et al., In vivo retargeting of T cell effector function by recombinant bispecific single chain Fv (anti-CD3 x anti-idiotype) induces long-term survival in the murine BCL1 lymphoma model., J. Immunol., 1998, Vol. 161, No. 3, pages 1454-1461
Document 4:.
MALLENDER WD. et al., Construction, expression, and activity of a bivalent bispecific single-chain antibody., J. Biol. Chem., 1994, Vol. 269, No. 1, pages 199-206
Document 5:
MACK M. et al., A small bispecific antibody construct expressed as a functional single-chain molecule with high tumor cell cytotoxicity., Proc. Natl. Acad. Sci. USA., 1995, Vol. 92, No. 15, pages 7021-7025
Document 6.
ORITA, T. et al., A novel therapeutic approach for thrombocytopenia by minibody agonist of the thrombopoietin receptor., Blood, 15 January 2005, Vol. 105, No. 2, pages 562-566

(Continued in supplemental box)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306800

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V.2

•Claims 1, 2, 5, 6, 8, 9-12, 14-17, and 19-22

Documents 1-3 state that incorrect Fv combinations occur in bispecific sc(Fv)2 antibodies.

Documents 1-3 do not mention the intention to eliminate bispecific sc(Fv)2 antibodies formed by erroneous combinations of such VH and VL fragments (hereinafter, "erroneous bispecific sc(Fv)2"). However, this authority finds that persons skilled in the art will naturally recall that such an "erroneous bispecific sc(Fv)2" antibody will lose its original antigen binding capability and should not be present together with the original "bispecific sc(Fv)2."

This being the case, this authority finds that persons skilled in the art can easily conceive of trying to eliminate such "erroneous bispecific sc(Fv)2" antibodies by performing an affinity purification procedure using a bispecific antigen corresponding to the original "bispecific sc(Fv)2" as described in document 4. In addition, this authority finds that persons skilled in the art can attempt to use a substance purified thereby as a pharmaceutical composition and the like in accordance with the properties thereof as needed.

In this context, judging from the statements in the DESCRIPTION of this application, bispecific substances are included in the scope of the terms "sc(Fv)2," "single chain diabody," and "bivalent scFv" in the claims, and because the aforementioned original "bispecific sc(Fv)2" and the "erroneous bispecific sc(Fv)2" are related as "structural isomers" referred to in the DESCRIPTION of this application, this authority finds that essentially performing the aforementioned affinity purification procedure corresponds to the step wherein structural isomers in an sc(Fv)2 composition are separated, and a specific structural isomer is acquired.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-4, and therefore these inventions lack an inventive step.

•Claims 3, 4, 7, 13, and 39-43

Document 1 states that when the linker connecting two scFv fragments is long, for example 15 amino acids or longer, the likelihood that the antibody will become an "erroneous bispecific sc(Fv)2" is increased by the flexibility of that linker. In addition, documents 5 and 6 specifically describe linkers comprising 15 amino acids.
(Continued in supplemental box)

V. 2

In this context, this authority finds that persons skilled in the art familiar with these descriptions will naturally recall adjusting the linker length so that a desired bispecific sc(Fv)2 will be formed as much as possible.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-6, and therefore these inventions lack an inventive step.

•Claims 18 and 44

Figure 1A of document 3 shows that an original "bispecific sc(Fv)2" and "erroneous bispecific sc(Fv)2) are detected as different bands in an SDS-PAGE procedure.

This being the case, this authority finds that persons skilled in the art will naturally recall attempting separation based on the differences in physical properties between original "bispecific sc(Fv)2" and "erroneous bispecific sc(Fv)2" antibodies. In addition, this authority finds that persons skilled in the art can attempt to discover structural differences therein from the enzymatic degradation products thereof and the like as needed.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-4, and therefore these inventions lack an inventive step.

•Claims 23-38

Performing substitutions and the like in part of the amino acid sequence of a mutually interacting protein and changing the mode of mutual interaction thereby was widely known technology to persons skilled in the art before the priority date of this application.

In this context, this authority finds that the structure of the variable region of the antibody was investigated in detail before the priority date of this application, and based on that knowledge, persons skilled in the art could perform amino acid substitutions as needed such that as few "erroneous bispecific sc(Fv)2" antibodies as possible will be formed.

In addition, this authority finds that no particularly outstanding effect is provided by adopting the constituent elements of the inventions of the above claims.

As a result, this authority finds that persons skilled in the art could easily arrive at the inventions of the above claims based on the descriptions in documents 1-6, and therefore these inventions lack an inventive step.